REMARKS

In view of the following remarks, the Examiner is requested to allow Claims 1-2, 5-15, 17-33, 36-40, 102-116, 119-129, 131-136, 139-163, and 165, the only claims pending and under examination in this application.

Claims 16, 34-35, 117-118, 130, 137-138 and 164 have been canceled without prejudice.

Claims 1, 102, 122, 148 and 157 have been amended to clarify the claim language. No new matter has been added.

Claim Rejections – 35 U.S.C. § 112

Claims 16, 33-36, 116-118, 130, 136-138 and 164 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The test for definiteness under 35 U.S.C. § 112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986).

As indicated above, Claims 16, 34-35, 117-118, 130, 137-138 and 164 have been canceled. Thus, the rejection of these claims under 35 U.S.C. § 112, second paragraph is rendered moot and may be withdrawn.

Claims 33, 116 and 136 include the element that the subsequence is at least three nucleotides from the terminus of the oligonucleotides. The Applicants respectfully submit that one of skill in the art would understand how to determine the terminus of an oligonucleotide and also how to determine whether the subsequence is at least three nucleotides from the terminus. As such, Claims 33, 166 and 136 satisfy the definiteness requirement of 35 U.S.C. § 112, second paragraph, and this rejection may be withdrawn.

Claim 36 includes the element that the association free energy of the members of a set of subsequences within each of the oligonucleotides is determined and the subsequence having the minimum value is identified. The Applicants respectfully submit that one of skill in the art would understand how to determine the

association free energy of the subsequences and how to identify the subsequence having the minimum value. As illustrated on page 21, lines 10-32, page 51, lines 5-8, and page 51, lines 24-28, free energy of duplex formation is a thermodynamic factor that may be determined for the most stable association between a subsequence and a target sequence. Thus, the Applicants submit that Claim 36 satisfies the definiteness requirement of 35 U.S.C. § 112, second paragraph, and respectfully request withdrawal of this rejection.

Claim Rejections – 35 U.S.C. § 101

Claims 1, 2, 5-25, 27-40 and 102-165 were rejected under 35 U.S.C. § 101 for allegedly being directed to non-statutory subject matter. In making this rejection, the Examiner alleges that "as claimed, the method does not produce a tangible result" and that "the method as claimed may take place entirely within the confines of a computer or a human mind without any communication to the outside world and without using or making available for use, the results of the computation." Office Action, pg. 5, last paragraph.

As set forth above, Claims 1, 102, 122, 148 and 157 have been amended to clarify the claim language. Specifically, the step (f) of each claim has been amended to read as follows "(f) outputting results of said selecting of step (e) in a human-readable form." Claims 2, 5-25, 27-40, 103-121, 123-147, 149-156, and 158-165 ultimately depend from the amended claims. As such, the Applicants submit that this rejection has been adequately addressed and thus, respectfully request withdrawal of the 35 U.S.C. § 101 rejection of Claims 1, 2, 5-25, 27-40 and 102-165.

Claim Rejections – 35 U.S.C. § 103

Rejection #1

Claims 1, 5-6, 10, 15, 17, 21, 24, 37-38, 122, 124-129, 131-133, 139, 144-145, 157, 159-163 and 165 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cronin et al. (*Human Mutation*, vol. 7, 1996, pg. 244-255), in view of Hyndman et al. (*Biotechniques*, vol. 20, 1996, pg. 1090-1095).

In order to meet its burden in establishing a rejection under 35 U.S.C. § 103, the Office must first demonstrate that a prior art reference, or references when

combined, teach or suggest all claim elements. *See e.g.*, *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all the elements were known in the prior art, the Office must also articulate a reason for combining the elements. *See e.g.*, *KSR*, 127 S.Ct. at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) (citing *KSR*). Further, the Supreme Court in *KSR* also stated that that "a court *must* ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR*, 127 S.Ct. at 1740 (emphasis added). As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

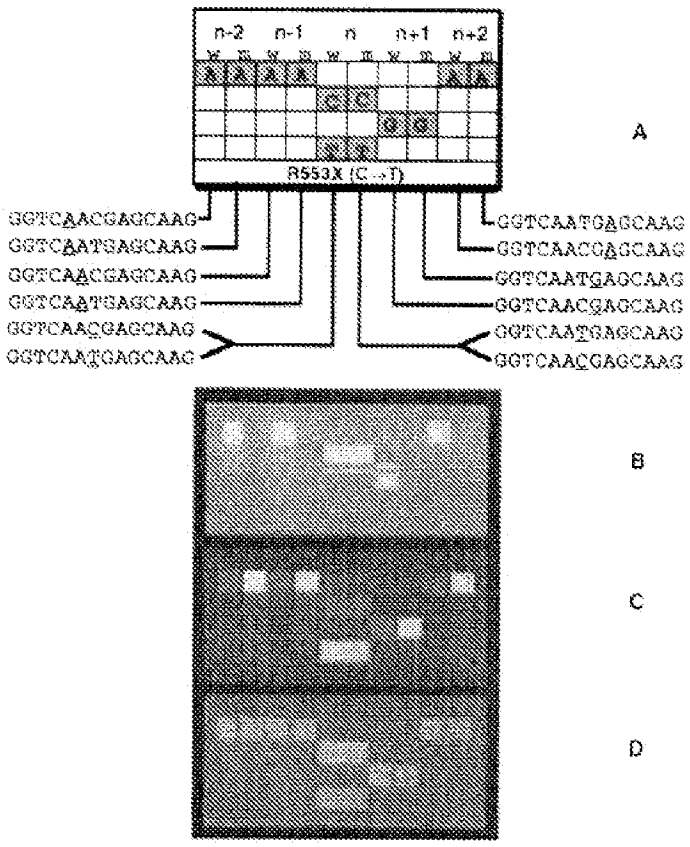
Independent Claims 1, 122 and 157 are directed to computer based methods for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. Independent Claims 1, 122 and 157 include the elements of: (d) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence; and (e) selecting, for a cluster of step (d), a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization oligonucleotide in said cluster.

In making the instant rejection, the Examiner alleges that "The caption of Figure 3 of Cronin et al. selects a single sequence from among the nucleotides in the cluster." It appears the Examiner is attempting to equate this alleged disclosure in Cronin with the Applicants' claimed elements of (d) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence, and (e) selecting, for a cluster of step (d), a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization oligonucleotide in said cluster.

The Applicants respectfully disagree. Cronin actually discloses a "hybridization array [that] characterizes specific mutations by using smaller, specialized probe arrays, termed mutation arrays. Each mutation array is composed

of two parallel probe sets, one set complementary to the wild-type gene sequence and the other complementary to a given mutant sequence." Cronin, pg 245-246, bridging paragraph; and Figure 3. In addition, Cronin discloses "DNA samples to be sequence checked, termed DNA targets, are fluorescently labeled and hybridized to the probe arrays under conditions promoting perfect match duplex stability and mismatched duplex instability. Fluorescent hybridization signals from features within the probe array then translate into target sequence. This format enables specific, highly parallel CFTR mutation analysis for homozygous and heterozygous genomic samples even in the context of other local polymorphisms." Cronin, pg. 246, col. 1, first full paragraph; and Figure 3.

As seen with reference to Figure 3, shown below, Cronin discloses the fluorescence images of a hybridization with an oligonucleotide target matching the wild-type sequence (see Figure 3(B)), a hybridization with an oligonucleotide target matching the mutant sequence (see Figure 3(C)), and a hybridization with both wild-type and mutant oligonucleotide targets (see Figure 3(D)).



Thus, Cronin merely discloses "specific, highly parallel CFTR mutation analysis for homozygous and heterozygous genomic samples". Consequently, Cronin does not disclose or suggest the Applicants' claimed elements of (d) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence, and (e) selecting, for a cluster of step (d), a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization oligonucleotide in said cluster.

In addition, the Examiner concedes that Cronin "fails to teach the 'computer aspects' to the instant set of data (i.e. computer determination of hybridization intensities)." Office Action, pg. 8, ¶ 3. Thus, to remedy this deficiency in Cronin, the Examiner relies upon Hyndman's alleged disclosure of software to determine optimal oligonucleotide sequences based on hybridization simulations data. However, Hyndman fails to remedy the deficiencies in Cronin, as discussed above.

Therefore, the Applicants submit that the cited combination of Cronin and Hyndman fails to disclose or suggest all the elements of the Applicants' claimed invention. As such, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 5-6, 10, 15, 17, 21, 24, 37-38, 122, 124-129, 131-133, 139, 144-145, 157, 159-163 and 165 be withdrawn.

Rejection #2

Claims 18-20 and 22 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cronin et al., in view of Hyndman et al., in further view of Southern (*Nucleic Acids Research*, 1994, vol. 22, pg. 1368-1373) (hereinafter "Southern (1994)").

As set forth above, Cronin in view of Hyndman is deficient in that they fail to disclose or suggest the claimed elements of (d) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence, and (e) selecting, for a cluster of step (d), a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization

oligonucleotide in said cluster. Southern (1994) was cited solely for its alleged disclosure of DNA, RNA and modified oligonucleotides. Consequently, Southern (1994) fails to remedy the deficiencies of Cronin and Hyndman. Therefore, the cited combination of Cronin, Hyndman and Southern (1994) does not disclose or suggest all the elements of Claims 18-20 and 22, and the Applicants respectfully request withdrawal of this rejection.

Rejection #3

Claims 2, 11-13, 39-40, 102-109, 111-113, 120, 121, 123, 140-143, 148-153, 155-156 and 158 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cronin et al., in view of Hyndman et al., in further view of Southern (*Genomics*, 1992, vol. 13, pg. 1008-1017) (hereinafter "Southern (1992)").

As set forth above, Cronin in view of Hyndman is deficient in that they fail to disclose or suggest the claimed elements of (d) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence, and (e) selecting, for a cluster of step (d), a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization oligonucleotide in said cluster. Southern (1992) was cited solely for its alleged disclosure of ranking of the nucleotides. Consequently, Southern (1992) fails to remedy the deficiencies of Cronin and Hyndman. Therefore, the cited combination of Cronin, Hyndman and Southern (1992) does not disclose or suggest all the elements of Claims 2, 11-13, 39-40, 102-109, 111-113, 120, 121, 123, 140-143, 148-153, 155-156 and 158, and the Applicants respectfully request withdrawal of this rejection.

Rejection #4

Claims 7, 23, 30-32 and 134-135 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cronin et al., in view of Hyndman et al., in further view of Petersheim et al. (*Biochemistry*, 1983, vol. 22, pg. 256-263).

As set forth above, Cronin in view of Hyndman is deficient in that they fail to disclose or suggest the claimed elements of (d) identifying oligonucleotides in said

subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence, and (e) selecting, for a cluster of step (d), a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization oligonucleotide in said cluster. Petersheim was cited solely for its alleged disclosure of the thermodynamic parameters (free energy, melting temperature, entropy, and enthalpy) for duplex formation. Consequently, Petersheim fails to remedy the deficiencies of Cronin and Hyndman. Therefore, the cited combination of Cronin, Hyndman and Petershein does not disclose or suggest all the elements of Claims 7, 23, 30-32 and 134-135, and the Applicants respectfully request withdrawal of this rejection.

Rejection #5

Claims 8-9 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cronin et al., in view of Hyndman et al., in further view of McMahon et al. (U.S. Patent No. 5,310,650).

As set forth above, Cronin in view of Hyndman is deficient in that they fail to disclose or suggest the claimed elements of (d) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence, and (e) selecting, for a cluster of step (d), a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization oligonucleotide in said cluster. McMahon was cited solely for its alleged disclosure of kinetics and coupling efficiencies of hybridizations. Consequently, McMahon fails to remedy the deficiencies of Cronin and Hyndman. Therefore, the cited combination of Cronin, Hyndman and McMahon does not disclose or suggest all the elements of Claims 8-9, and the Applicants respectfully request withdrawal of this rejection.

Rejection #6

Claims 114-115 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cronin et al., in view of Hyndman et al., in view of Southern (1992), and further in view of Petersheim.

As set forth above, Cronin in view of Hyndman is deficient in that they fail to disclose or suggest the claimed elements of (d) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence, and (e) selecting, for a cluster of step (d), a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization oligonucleotide in said cluster. The Examiner concedes that the cited combination of Cronin, Hyndman and Southern (1992) fails to make obvious the clustering and ranking of tiled probe arrays, and the relevant parameter of free energy. Petersheim was cited solely for its alleged disclosure of thermodynamic analysis and thermodynamic parameters. However, Southern (1992) and Petersheim fail to remedy the deficiencies of Cronin and Hyndman, as discussed above. Therefore, the cited combination of Cronin, Hyndman, Southern (1992) and Petersheim does not disclose or suggest all the elements of Claims 114-115, and the Applicants respectfully request withdrawal of this rejection.

Rejection #7

Claim 14 was rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cronin et al., in view of Hyndman et al., in further view of Anderson et al. (*Introduction to Statistics*, New York: West Publishing Company, 1991, pg. 64-65).

As set forth above, Cronin in view of Hyndman is deficient in that they fail to disclose or suggest the claimed elements of (d) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence, and (e) selecting, for a cluster of step (d), a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization oligonucleotide in said cluster. Anderson was cited solely for its alleged disclosure of

dividing data into four quartiles. Consequently, Anderson fails to remedy the deficiencies of Cronin and Hyndman. Therefore, the cited combination of Cronin, Hyndman and Anderson does not disclose or suggest all the elements of Claim 14, and the Applicants respectfully request withdrawal of this rejection.

Rejection #8

Claims 25 and 27 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cronin et al., in view of Hyndman et al., in further view of Anton (*Elementary Linear Algebra*, New York: John Wiley and Sons, 1987, pg. 35-37).

As set forth above, Cronin in view of Hyndman is deficient in that they fail to disclose or suggest the claimed elements of (d) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence, and (e) selecting, for a cluster of step (d), a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization oligonucleotide in said cluster. Anton was cited solely for its alleged disclosure of the use and properties of identity matrices. Consequently, Anton fails to remedy the deficiencies of Cronin and Hyndman. Therefore, the cited combination of Cronin, Hyndman and Anton does not disclose or suggest all the elements of Claims 25 and 27, and the Applicants respectfully request withdrawal of this rejection.

Rejection #9

Claims 28-29 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cronin et al., in view of Hyndman et al., in further view of Edwards (*An Introduction to Linear Regression and Correlation*; New York: W.H. Freeman and Co., 1984, pg. 24-26).

As set forth above, Cronin in view of Hyndman is deficient in that they fail to disclose or suggest the claimed elements of (d) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence, and (e) selecting, for a cluster of step (d), a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization

oligonucleotide in said cluster. Edwards was cited solely for its alleged disclosure of the theory behind correlation coefficients. Consequently, Edwards fails to remedy the deficiencies of Cronin and Hyndman. Therefore, the cited combination of Cronin, Hyndman and Edwards does not disclose or suggest all the elements of Claims 28-29, and the Applicants respectfully request withdrawal of this rejection.

Rejection #10

Claims 16, 130 and 164 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cronin et al., in view of Hyndman et al., in further view of Goldberg et al. (U.S. Patent No. 5,959,098).

As set forth above, Claims 16, 130 and 164 have been canceled without prejudice. Consequently, this rejection is rendered moot and may be withdrawn.

Rejection #11

Claims 110 and 154 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cronin et al., in view of Hyndman et al., in view of Southern (1992), and in further view of Goldberg et al. (U.S. Patent No. 5,959,098).

As set forth above, Cronin in view of Hyndman is deficient in that they fail to disclose or suggest the claimed elements of (d) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence, and (e) selecting, for a cluster of step (d), a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization oligonucleotide in said cluster. The Examiner concedes that the cited combination of Cronin, Hyndman and Southern (1992) fails to make obvious the attachment of the oligonucleotides to a surface. Goldberg was cited solely for its alleged disclosure of the attachment of the oligonucleotides to a surface. However, Southern (1992) and Goldberg fail to remedy the deficiencies of Cronin and Hyndman, as discussed above. Therefore, the cited combination of Cronin, Hyndman, Southern (1992) and Goldberg does not disclose or suggest all the elements of Claims 110 and 154, and the Applicants respectfully request withdrawal of this rejection.

Rejection #12

Claims 116-118 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cronin et al., in view of Hyndman et al., in view of Southern (1992), in view of Petersheim, and in further view of Goldberg et al.

As set forth above, Cronin in view of Hyndman is deficient in that they fail to disclose or suggest the claimed elements of (d) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence, and (e) selecting, for a cluster of step (d), a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization oligonucleotide in said cluster. The Examiner concedes that the cited combination of Cronin, Hyndman, Southern (1992), and Petersheim fails to make obvious the attachment of the oligonucleotides to a surface with the appropriate recited distances. Goldberg was cited solely for its alleged disclosure of the attachment of the oligonucleotides to a surface. However, Southern (1992), Petersheim and Goldberg fail to remedy the deficiencies of Cronin and Hyndman, as discussed above. Therefore, the cited combination of Cronin, Hyndman, Southern (1992), Petersheim and Goldberg does not disclose or suggest all the elements of Claims 116-118, and the Applicants respectfully request withdrawal of this rejection.

Rejection #13

Claims 33-36 and 136-138 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cronin et al., in view of Hyndman et al., in view of Petersheim, and in further view of Goldberg et al.

As set forth above, Cronin in view of Hyndman is deficient in that they fail to disclose or suggest the claimed elements of (d) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence, and (e) selecting, for a cluster of step (d), a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization oligonucleotide in said cluster. The Examiner concedes that the cited combination of Cronin, Hyndman, and Petersheim fails to make obvious the attachment of the

oligonucleotides to a surface. Goldberg was cited solely for its alleged disclosure of the attachment of the oligonucleotides to a surface. However, Petersheim and Goldberg fail to remedy the deficiencies of Cronin and Hyndman, as discussed above. Therefore, the cited combination of Cronin, Hyndman, Petersheim and Goldberg does not disclose or suggest all the elements of Claims 33-36 and 136-138, and the Applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret Field at (650) 327-3400.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10971464-3.

Respectfully submitted,

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